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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/830,779 | 11/30/2001 | Kenneth Chien | 6627-PA9025 | 3690 |

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MORRISON & FOERSTER LLP
3811 VALLEY CENTRE DRIVE
SUITE 500
SAN DIEGO, CA 92130-2332

| EXAMINER | |
|---|---|
| DUFFY, PATRICIA ANN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

DATE MAILED: 12/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/830,779 | CHIEN ET AL. | |
| | Examiner | Art Unit | |
| | Patricia A. Duffy | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *9-4-04 AND 9-17-04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4,12,16,19,20 and 22-45* is/are pending in the application.

4a) Of the above claim(s) *24-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,12,19,20,22,23 and 40-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

*Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 9-4-04 and 9-17-04 have been entered.

The amendment filed 9-17-04 has been entered into the record. The declaration filed June 1, 2004 has been entered into the record. Claims 1, 4, 12, 16, 19, 20 and 22-45 are pending. Claims 1, 4, 12, 16, 19, 20, 22, 23 and 40-45 are under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

*Election/Restrictions*

Claims 24-39 are withdrawn as being drawn to a non-elected invention as lacking unity of invention. The new claims drawn to gene therapy lack unity of invention with protein therapy as they are not drawn to the same technical feature (protein versus nucleic acid) and the technical feature of claims 24-39 is anticipated by the art as set forth in the International Preliminary Examination Report (Dillman et al of record). Therefore, the claims directed to protein administration versus nucleic acid administration lack unity of invention because the technical feature of the latter is known in the art and therefore the inventions are not linked by a technical feature that is "special" within the meaning of PCT Rule 13.2.

*Rejections Withdrawn*

Any rejection not explicitly maintained herein is withdrawn based on Applicants amendments.

*Rejections Maintained*

Claims 1, 4, 12, 16, 19, 20, 22, 23 and 40-45 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons made of record in the office actions mailed 06-03-03 and 1-20-04.

Applicants' arguments and declarations have been carefully considered but are not persuasive. Applicants' arguments are misdirected. The claims are drawn to a method of treatment of heart failure comprising attenuating PLB-induced cardiac SR Ca2+ ATPase inhibition and enhancing contractility in a heart comprising administering a compound comprising an exogenous dominant negative phospholamban protein functionally attached to a transport peptide and contacting the heart with the compound. The claims under examination are not drawn to gene therapy and the methodology, principles and pharmacology of protein administration versus nucleic acid administration are quite different and cannot be equated. While gene therapy provides for a constant expression of the drug inside the target cell, protein therapy does not. Applicants are again arguing different embodiments of the invention to support a conclusion that one of skill in the art could get the invention to work, despite the specifically articulated finding of Applicants in their own specification that there was NO STATICALLY SIGNIFICANT effect on the heart in treated animals of the specification. It did not increase cardiac contractility to any significant result. The claims are not drawn to *in vitro* treating of isolated cardiac myocytes and are not drawn to gene therapy, but *in vivo* treatment to expressly provide for treatment of heart failure. The question remains.... does the specification as filed, teach the skilled artisan how to successfully administer of any claimed dominant negative PLB proteins functionally linked to a transport peptide for the treatment of heart failure.

This application fails to teach how to use the claimed protein based therapeutic to treat heart failure as claimed. Applicants and Declarant allege that one skilled in the art could essentially get the invention to work based on the demonstrated effect on isolated cardiac myocytes, gene therapy results and high skill in the art. This is not persuasive. The courts have held that the disclosure is insufficient when testing is necessary to determine the actual use or possible lack of use *(In re Kirk and Petrow* (CCPA) 153 USPQ 48). Reliance on the skill of the art for routine screening would not be persuasive to remove this rejection because; as also recognized by the Federal Circuit: "However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement..... . It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research." ( Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001). Further, routine screening for an enabled embodiment is not the legal standard. There is no routine screening when there is no predictability in the screen. Applicants own work indicates no statistically significant results and therefore were is the predictability to find something that works, when the expert in the art cannot set forth any embodiment that is effective as claimed. Declarant's opinion relies upon the teachings of the specification that have already been considered but does not obviate the facts as set forth in the specification that *in vivo* the claimed application does not work. It is clear that no statistically significant results were achieved using any protein based therapeutic in the *in vivo* assay. Declarant provides no factual evidence in the declaration that is not present in the specification as filed. The fact remains that the specification does not enable treatment *in vivo* for heart disease using any of the claimed PLB dominant negative mutants, the only *in vivo* test failed. This indicates that for the protein based therapeutic there is no correlation between the *in vitro* results and the *in vivo*

therapeutic benefit. The specification and Declarant merely provides for an invitation to experiment to the skilled artisan to attempt to find a modality that may or may not work, and this additional work is in fact the essence of invention. It is Applicant that must enable the invention.

The rejection is maintained for all the reasons made of record and those herein.

Claims 1, 4, 12, 16, 19, 20, 22, 23 and 40-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons made of record.

Applicants point to Example 4 of the specification. Example 4 does not provide for conception of the genus of "dominant negative PLB polypeptides" as set forth in the claims. Whether or not someone of skill in the art could derive others is not the issue. The issue is whether the now claimed genus is supported by the specification as filed. Example 4, does not teach nor describe the genus of "dominant negative" PLB polypeptides. Further, Declarant's assertion of a textbook definition of dominant negative is not persuasive because the textbook has not been presented as extrinsic evidence of a definition in the art at the time that the invention was made. The relevant textbook, dates, pages have not been provided and therefore is viewed at this point as an assertion of a teaching that cannot be independently verified by evidence of record. This rejection is maintained.

Additionally, while the specification teaches the subgenus of covalent linkage of the penetrating peptide to the PLB by means of covalent peptide linkages, the generic term "functional linked" encompasses any means of functionally linking the recited members. These means include, for example, non-covalent and chemical linkages. These functional linkages were not conceived in the specification as filed. Therefore, the

specification as originally filed fails to provide written description support for conception of the genus of "functional linkage" as is now claimed and as such introduce new concepts. In re East and Harmon (CCPA) 181 USPQ 716 (May 9, 1994). This portion of the rejection was not addressed and is maintained for reasons made of record.

Claims 1, 4, 12, 16, 19, 20, 22, 23 and 40-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recited an exogenous "dominant negative" phospholamban (PLB) protein functionally attached to a penetratin peptide". Dominant negative is discussed as a phenotypic effect upon a cell and a relative term to some normal situation. The term is not described in terms of a polypeptide by the phenotypic effect exerted by the administered polypeptide relative to a polypeptide that is not set forth in the claims. Declarant asserts a textbook definition of dominant negative is not persuasive because the textbook has not been presented as extrinsic evidence of a definition in the art at the time that the invention was made. The relevant textbook, dates, pages have not been provided and therefore is viewed at this point as an assertion of a teaching that cannot be independently verified by evidence of record. This rejection is maintained.

***New Rejections Based on Amendment***

Claim 1, 4, 12, 16, 19, 20, 22, 23, 40-42 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants have amended the claims to broadly recite "transport peptide", this term is viewed to encompass any transport peptide, that functions to transport anything either by receptor mediated transport or receptor-independent transport or by any other conceivable means. The specification describes at best specific transport peptides that are receptor-independent. The specification does not describe or conceive of receptor-dependent transport mechanisms or by or conceived means. If the written description does not use precisely the same terms used in a claim, the question then is whether the specification directs or guides one skilled in the art to the subject matter claimed. See, e.g., Fujikawa v. Wattanasin, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996). The specification as filed fails to conceive of the now claimed genus in the written description of the invention as originally filed. The courts have spoken on similar issues where Applicants broaden the claims to encompass a genus that is not contemplated by the written description as filed. In *In re East and Harmon* (CCPA) 181 USPQ 716 (May 9, 1994), the claims of a reissue application are drawn to new matter since they broadly recite genus of "carrier particles" which is not disclosed in original patent, which discloses only subgenus of "magnetic carrier particles" and species of "iron, ferrites, nickel, and cobalt" carrier particles. Similarly, in the instant case the specification only discloses a subgenus of receptor-independent transport peptides.

## *Status of Claims*

Claims 1, 4, 12, 16, 19, 20, 22, 23 and 40-45 stand rejected. Claims 24-39 are withdrawn from consideration.

## *Conclusion*

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy

Primary Examiner

Art Unit 1645